

United States Patent and Trademark Office



UNITED STATES DEPARTMENT OF COMMERCE United States Patent and Trademark Office Address: COMMISSIONER FOR PATENTS P.O. Box 1450 Alexandria, Virginia 22313-1450 www.uspto.gov

APPLICATION NO.	F	TLING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.	
09/701,583	701,583 02/05/2001		Karl-Hermann Schlingensiepen	P66141US0	7033	
136	7590	04/04/2005		EXAMINER		
		IAN PLLC	ZARA, JANE J			
400 SEVEN SUITE 600	IHSIRE	EI N.W.		ART UNIT	PAPER NUMBER	
WASHING	ron, do	20004		1635		
				DATE MAILED: 04/04/2005		

Please find below and/or attached an Office communication concerning this application or proceeding.

		Applica	ition No.	Applicant(s)		
		09/701	,583	SCHLINGENSIE	SCHLINGENSIEPEN ET AL.	
	Office Action Summary	Examir	ner .	Art Unit		
		Jane Za		1635		
Period fo	- The MAILING DATE of this commun r Reply	nication appears on t	the cover sheet with	the correspondence a	ddress	
THE N - Exten after S - If the - If NO - Failur Any re	DRTENED STATUTORY PERIOD F MAILING DATE OF THIS COMMUN sions of time may be available under the provisions SiX (6) MONTHS from the mailing date of this comi period for reply specified above, the maximum s e to reply within the set or extended period for reply eply received by the Office later than three months d patent term adjustment. See 37 CFR 1.704(b).	ICATION. s of 37 CFR 1.136(a). In no nunication. s0) days, a reply within the statutory period will apply and will, by statute, cause the a	event, however, may a reply tatutory minimum of thirty (3 I will expire SIX (6) MONTH application to become ABAN	y be timely filed 30) days will be considered time S from the mailing date of this DONED (35 U.S.C. § 133).	∍ly. communication.	
Status						
1)⊠	Responsive to communication(s) file	ed on <u>14 January 20</u>	<u>005</u> .			
2a) <u></u> □	This action is FINAL.	2b)⊠ This action is	non-final.			
	Since this application is in condition for allowance except for formal matters, prosecution as to the ments is closed in accordance with the practice under <i>Ex parte Quayle</i> , 1935 C.D. 11, 453 O.G. 213.					
Disposition	on of Claims					
5)□ 6)⊠ 7)□	Claim(s) <u>1-11</u> is/are pending in the 4a) Of the above claim(s) <u>6</u> is/are with Claim(s) <u>1-5 and 7-11</u> is/are rejected Claim(s) <u>1-5 and 7-11</u> is/are rejected to. Claim(s) <u>are subject to restricted to the claim(s) are subject to restricted to the claim(s) <u>are subject to restricted to the claim(s) <u>are subject to restricted to the claim(s) <u>are subject to restricted to the claim(s) are subject to restricted to the claim(s) <u>are subject to restricted to the claim(s) are subject to the </u></u></u></u></u>	thdrawn from consid				
Application	on Papers					
9)[] 7	The specification is objected to by th	e Examiner.				
10) 🗌 🗆	The drawing(s) filed on is/are	: a)□ accepted or	b)□ objected to by	the Examiner.		
	Applicant may not request that any obje	ction to the drawing(s) be held in abeyance	. See 37 CFR 1.85(a).		
	Replacement drawing sheet(s) including The oath or declaration is objected t			=	• •	
Priority u	nder 35 U.S.C. § 119					
a)∑	Acknowledgment is made of a claim All b) Some * c) None of: 1. Certified copies of the priority Certified copies of the priority Copies of the certified copies application from the Internation	documents have be documents have be of the priority docur anal Bureau (PCT R	een received. een received in App ments have been re ule 17.2(a)).	lication No ceived in this National	l Stage	
Attachment(· •			(DTC 442)		
	of References Cited (PTO-892) of Draftsperson's Patent Drawing Review (F	PTO-948)	4) Interview Sum Paper No(s)/M	nmary (PTO-413) 1ail Date		
3) 🔯 Inform	ation Disclosure Statement(s) (PTO-1449 or No(s)/Mail Date <u>4-25-01</u> .		5) Notice of Infor 6) Other: 5.	mal Patent Application (PT	O-152)	

Application/Control Number: 09/701,583

Art Unit: 1635

DETAILED ACTION

This Office action is in response to the communication filed 1-14-05.

Claims 1-11 are pending in the instant application.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Response to Arguments and Amendments

Withdrawn Rejections

Any rejections not repeated in this Office action are hereby withdrawn.

Maintained Rejections

Claims 1-4, 7, 8 and 9 are rejected under 35 U.S.C. 102(b) as being anticipated by Fakhrai et al for the same reasons of record set forth in the Office action mailed 7-14-04.

Applicant's arguments filed 1-14-05 have been fully considered but they are not persuasive. Applicants argue that Fakhrai does not anticipate the instantly claimed invention because this reference does not explicitly disclose a combination of both an inhibitor of an immunosuppressant and an immunostimulator as a medicament.

Contrary to Applicant's assertions, the claimed invention is drawn to compositions for the treatment of neoplasms comprising at least one inhibitor of an immune suppressor (e.g. antisense targeting and inhibiting the expression of TGF-beta or its receptors) and one immune stimulator. Fakhrai teaches the administration of glioma cells that have

been transfected with antisense which target and inhibit the expression of a nucleic acid encoding a TGF-beta molecule (see p. 2909 or Fakhrai, left col., "Glioma cells express major histocompatibility complex class I and class II molecules... as well as tumorassociated antigens that have been demonstrated to stimulate anti-tumor immune responses and thus are good tumor vaccine candidates... However, several studies have demonstrated the secretion of an immunosuppressive factor by glioma cells that was subsequently identified as transforming growth factor [beta]." Therefore, by administering these anti-TGF-beta- antisense transfected, tumor antigen-expressing, glioma cells to organisms which are afflicted to brain tumors, Fakhrai anticipates the instantly claimed invention.

Page 3

Claims 1-4, 7, 8 and 9 are rejected under 35 U.S.C. 102(e) as being anticipated by Caniggia et al for the same reasons of record set forth in the Office action mailed 7-14-04. Applicants argue that Caniggia does not qualify as prior art for several reasons. These reasons include the fact that the Caniggia reference (USPN 6,376,199) has a 102(e) date of Dec. 21, 1999. Applicants are correct that this date has been provided as the 102(e) date of USPN 6,376,199, which claimed priority to the PCT document WO98/40747. But the priority data for USPN 6,376,199 includes the provisional document 60/039,919, filed on 3-7-97. This provisional document predates the priority date of the instantly claimed invention. Moreover, the provisional application, on pp. 12-13, provides the teaching that anticipates the instant invention:

The compositions of the invention contain at least one inhibitor or stimulator of a cytokine of the TGF-beta family or receptors of cytokines of the TGF-beta family, preferably an inhibitor of TGF-beta3 or its receptor, alone or together with other active substances... The compositions of the invention may be administered together with or prior to administration of other biological factors that have been found to affect trophoblast proliferation. Examples of these factors include IL-11... and G-CSF, GM-CSF and M-CSF...

Applicants argue that the language in Caniggia, which describes combining medicaments (e.g. cited above), is rather vague and therefore does not anticipate the claimed invention. Contrary to Applicant's assertions, the language of Caniggia clearly describes the option of administering compositions that combine antisense that target immunosuppressive agents including TGF-beta with immunostimulatory agents, including IL-11, G-CSF-GM-CSF and M-CSF.

New Rejections

Claim Objections

Claim 8 is objected to because of the following informalities: in line 5, "interleukins" is a misspelling. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-5 and 7-11 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are drawn to a pharmaceutical composition comprising at least one inhibitor of the effect of a substance that negatively effects an immune response, which substance is selected from TGF-beta and its receptors, VEGF and its receptors, IL-10 and its receptors, PGE-2 and its receptors, and which inhibitor inhibits the synthesis or function of the negative effector of an immune response, and which composition further comprises at least one stimulator positively effecting an immune response, which stimulator is enhancing the synthesis and/or function of factors selected from GM-CSF, SCF, CSF, IFN, FLT-3-ligand, monocyte chemotactic proteins, IL-2, IL-4, II-12 and/or IL-18, a virus, viral antigen, tumor or pathogenic antigen, or organ specific antigens expressed in affected organs but not essential for the organism or fusion of dendritic and tumor cells. The specification and claims do not indicate or adequately describe elements essential to the genera claimed, which genera include the negative effectors and stimulators claimed. The specification and claims do not indicate the distinguishing attributes concisely shared by the members of the genera comprising these negative effectors or stimulators. The disclosure does not clarify the common attributes that are encompassed by inhibitors of the synthesis or function of negative effectors of the immune system, and which negative effectors are selected from the group comprising

TGF-beta and its receptors, VEGF and its receptors, IL-10 and its receptors, PGE-2 and its receptors. The disclosure does not clarify the common attributes encompassed by stimulators that enhance the synthesis and/or function of GM-CSF, SCF, CSF, IFN, FLT-3-ligand, monocyte chemotactic proteins, IL-2, IL-4, II-12 and/or IL-18, a virus, viral antigen, tumor or pathogenic antigen, or organ specific antigens expressed in affected organs but not essential for the organism or fusion of dendritic and tumor cells. Furthermore, the disclosure does not adequately describe the attributes or concise characteristics encompassed by the genera comprising antigens, tumor or pathogenic antigens, or organ specific antigens expressed in affected organs but not essential for the organism or fusion of dendritic and tumor cells. Thus the scope of the claims includes numerous structural variants and the genera are highly variant because a significant number of structural differences between members of a given genus is permitted. Concise structural features that could distinguish structures or compounds within a genus from others are missing from the disclosure and the claims. The general knowledge and level of skill in the art do not supplement the omitted description because specific, not general guidance is what is needed. The specification fails to teach or adequately describe a representative number of species in each genera such that the common attributes or characteristics concisely identifying members of each proposed genera are exemplified. And because each genus is so highly variant, the description provided is insufficient. One of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the various genera claimed. Thus, Applicant was not in possession of the claimed genera.

Page 6

Application/Control Number: 09/701,583

Art Unit: 1635

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-5 and 7-11 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the in vitro inhibition of TGF-beta expression comprising the administration of antisense oligonucleotides, and for treating a brain neoplasia comprising the administration of an antisense and IL-2, which antisense targets and inhibits the expression of TGF-beta 2 as taught previously by Fakhrai et al, does not reasonably provide enablement for the targeting and inhibition of the TGF-beta family in vivo using antisense of SEQ ID NO: 7 or optionally in combination with a tumor cell extract, and which provides for treatment effects for neoplasia in an organism. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The claims are drawn to therapeutic (pharmaceutical) compositions for treating any neoplasm comprising the antisense oligonucleotide of SEQ ID NO: 7, or comprising at least one inhibitor of the effect of a substance that negatively effects an immune response, which substance is selected from TGF-beta and its receptors, VEGF and its receptors, IL-10 and its receptors, PGE-2 and its receptors, and which inhibitor inhibits the synthesis or function of the negative effector of an immune response, and which composition further comprises at least one stimulator positively effecting an immune

Art Unit: 1635

response, which stimulator enhances the synthesis and/or function of factors selected from GM-CSF, SCF, CSF, IFN, FLT-3-ligand, monocyte chemotactic proteins, IL-2, IL-4, II-12 and/or IL-18, a virus, viral antigen, tumor or pathogenic antigen, or organ specific antigens expressed in affected organs but not essential for the organism or fusion of dendritic and tumor cells.

The state of the prior art and the predictability or unpredictability of the art.

The following references are cited herein to illustrate the state of the art of nucleic acid treatment in organisms. Branch and Crooke teach that the in vivo (whole organism) application of nucleic acids (such as antisense) is a highly unpredictable endeavor due to target accessibility and delivery issues. Crooke also points out that cell culture examples are generally not predictive of in vivo inhibition of target genes. (A. Branch, Trends in Biochem. Sci. 23: 45-50; see entire text for Branch; S. Crooke, Antisense Res. and Application, Chapter 1, pp. 1-50, especially at 34-36).

Likewise, Peracchi cautions investigators in the field of gene therapy about the problems of achieving in vivo efficacy using oligonucleotide based approaches

Peracchi cites stability and delivery obstacles that need to be overcome in achieving desired in vivo efficacy: "A crucial limit of ribozymes in particular, and of oligonucleotide-based drugs in general, lies in their intrinsically low ability to cross biological membranes, and therefore to enter the cells where they are supposed to operate... cellular uptake following systemic administration appears to require more sophisticated formulations... the establishment of delivery systems that mediate

Page 9

efficient cellular uptake and sustained release of the ribozyme remains one of the major hurdles in the field." (A. Peracchi et al, Rev. Med. Virol., 14: 47-64, especially at 51).

Agrawal et al also speak to the unpredictable nature of the nucleic acid based therapy field thus: It is therefore appropriate to study each ... oligonucleotide in its own context, and relevant cell line, without generalizing the results for every oligonucleotide." (S. Agrawal et al., Molecular Med. Today, 6: 72-81 at 80). Cellular uptake of oligonucleotides by appropriate target cells is another rate limiting step that has yet to be overcome in achieving predictable clinical efficacy using antisense." Both Chirila et al and Agrawal et al point to the current limitations which exist in our understanding of the cellular uptake of ... oligonucleotides in vitro and in vivo (see Agrawal et al. especially at pages 79-80; see Chirila et al., Biomaterials, 23: 321-342 in its entirety, especially at 326-327 for a general review of the important and inordinately difficult challenge σ of the delivery of the rapeutic oligonucleotides to target cells).

The amount of direction or guidance presented in the specification AND the presence or absence of working examples. Applicants have not provided guidance in the specification toward a method of treating any neoplasm in an organism comprising the administration of any antisense, or comprising the administration of any inhibitor of the effect of a substance that negatively effects an immune response, which substance is selected from TGF-beta and its receptors, VEGF and its receptors, IL-10 and its receptors, PGE-2 and its receptors, and which inhibitor inhibits the synthesis or function of the negative effector of an immune response; nor have Applicants provided guidance in the specification toward a method of treating any neoplasm in an organism

comprising the co-administration of at least one stimulator positively effecting an immune response, which stimulator enhances the synthesis and/or function of factors selected from GM-CSF, SCF, CSF, IFN, FLT-3-ligand, monocyte chemotactic proteins, IL-2, IL-4, II-12 and/or IL-18, a virus, viral antigen, tumor or pathogenic antigen, or organ specific antigens expressed in affected organs but not essential for the organism or fusion of dendritic and tumor cells. The specification teaches the in vitro inhibition of TGF-beta expression using antisense. The specification also teaches the in vitro lysis of tumor cells following administration of antisense, GM-CSF and IL-4. One skilled in the art would not accept on its face the examples given in the specification of the in vitro inhibition of TGF-beta expression using antisense, or the in vitro lysis of tumor cells following administration of GM-CSF and IL-4 as being correlative or representative of the successful treatment of any neoplasia in an organism in view of the lack of guidance in the specification and known unpredictability associated with inhibition of a target gene in an organism using antisense and optionally additionally using tumor cell extract and further whereby treatment effects are provided for any neoplasia in that organism.

Page 10

The breadth of the claims and the quantity of experimentation required.

The breadth of the claims is very broad. The claims are drawn to therapeutic (pharmaceutical) compositions for treating any neoplasm comprising the antisense oligonucleotide of SEQ ID NO: 7, or comprising at least one inhibitor of the effect of a substance that negatively effects an immune response, which substance is selected from TGF-beta and its receptors, VEGF and its receptors, IL-10 and its receptors, PGE-2 and its receptors, and which inhibitor inhibits the synthesis or function of the negative

Page 11

Art Unit: 1635

effector of an immune response, and which composition further comprises at least one stimulator positively effecting an immune response, which stimulator enhances the synthesis and/or function of factors selected from GM-CSF, SCF, CSF, IFN, FLT-3ligand, monocyte chemotactic proteins, IL-2, IL-4, II-12 and/or IL-18, a virus, viral antigen, tumor or pathogenic antigen, or organ specific antigens expressed in affected organs, but not essential for the organism or fusion of dendritic and tumor cells. The quantity of experimentation required to practice the invention as claimed would require the de novo determination of accessible target sites, modes of delivery and formulations to target appropriate cells and /or tissues harboring the target TGF-beta sequence for antisense of SEQ ID NO: 7 in combination with administration of a tumor cell extract) whereby TGF-beta family gene expression is inhibited in cells in vivo and treatment effects are provided for any neoplasia. Also required for enabling the full scope claimed would be the de novo determination of accessible target sites, modes of delivery and formulations to target appropriate cells and/or tissues harboring a substance that negatively effects an immune response, which substance is selected from TGF-beta and its receptors, VEGF and its receptors, IL-10 and its receptors, PGE-2 and its receptors, whereby the synthesis or function of the negative effector of the immune response is inhibited upon administration of an inhibitor, and further whereby the synthesis and/or function of factors selected from GM-CSF, SCF, CSF, IFN, FLT-3ligand, monocyte chemotactic proteins, IL-2, IL-4, II-12 and/or IL-18, a virus, viral antigen, tumor or pathogenic antigen, or organ specific antigens expressed in affected organs, but not essential for the organism or fusion of dendritic and tumor cells, is

Art Unit: 1635

stimulated upon administration of a stimulator, and treatment effects for neoplasia are provided. Since the specification fails to provide any particular guidance for targeting appropriate cells harboring the target TGF-beta genes using antisense of SEQ ID NO: 7 in an organism, nor for providing any of the claimed inhibitory and stimulatory affects, whereby treatment effects for any neoplasia are provided, and since determination of these factors is highly unpredictable, it would require undue experimentation to practice the invention over the broad scope claimed.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless -

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 1-5, 7,8, 10 and 11 are rejected under 35 U.S.C. 102(a) as being anticipated by Schlingensiepen et al.

Schlingensiepen et al (WO 98/33904) teach pharmaceutical compositions comprising at least one inhibitor of an immune suppressor (e.g. antisense targeting and inhibiting the expression of TGF-beta or its receptors) and one immune stimulator (see pages 1, 2, 15, 27, figure 3-9, claims 12-15, and the accompanying sequence alignment data between SEQ ID NO: 528 of WO 98/33904 and SEQ ID NO: 7 or the instant application).

Art Unit: 1635

Double Patenting

A rejection based on double patenting of the "same invention" type finds its support in the language of 35 U.S.C. 101 which states that "whoever invents or discovers any new and useful process ... may obtain a patent therefor ..." (Emphasis added). Thus, the term "same invention," in this context, means an invention drawn to identical subject matter. See *Miller v. Eagle Mfg. Co.*, 151 U.S. 186 (1894); *In re Ockert*, 245 F.2d 467, 114 USPQ 330 (CCPA 1957); and *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970).

A statutory type (35 U.S.C. 101) double patenting rejection can be overcome by canceling or amending the conflicting claims so they are no longer coextensive in scope. The filing of a terminal disclaimer <u>cannot</u> overcome a double patenting rejection based upon 35 U.S.C. 101.

Claims 1-5, 7, 8, 10 and 11 are provisionally rejected under 35 U.S.C. 101 as claiming the same invention as that of claims 12-15 of copending Application No. 10/984,919. This is a <u>provisional</u> double patenting rejection since the conflicting claims have not in fact been patented. Both sets of claims are drawn to pharmaceutical compositions comprising at least one inhibitor of an immune suppressor (e.g. antisense targeting and inhibiting the expression of TGF-beta or its receptors) and one immune stimulator (see accompanying sequence alignment data of SEQ ID NO: 528 of 10/984,919 and SEQ ID NO. 7 of the instant application: They are the same oligonucleotide).

Conclusion

Certain papers related to this application may be submitted to Art Unit 1635 by facsimile transmission. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94

Application/Control Number: 09/701,583

Art Unit: 1635

(December 28, 1993) (see 37 C.F.R. → 1.6(d)). The official fax telephone number for the Group is **703-872-9306**. NOTE: If Applicant *does* submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Page 14

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Jane Zara** whose telephone number is **(571) 272-0765**. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader, can be reached on (571) 272-0760. Any inquiry regarding this application should be directed to the patent analyst, Katrina Turner, whose telephone number is (571) 272-0564. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

83 TC1600

JZ 3-28-05 ô

Tue Mar 8 14:45:12 2005

```
y CREANISM: Homo: sapiens
US-09-701-583A-7

Query Match
Best Local Similarity 100.0%; Score 19; DB 32; Length 19;
Best Local Similarity 100.0%; Pred: No. 69;
Matches 19; Conservative 0; Mismatches 0; Indels 0; Gaps

OY IGCTATTTGTAAACCTCC 19

IGTCTATTTGTAAACCTCC 19

IGTCTATTTTGTAAACCTCC 19

IGTCTATTTGTAAACCTCC 19

IGTCTATTTGTAAACCTCC 19

IGTCTATTTGTAAACCTCC 19

IGTCTATTTTGTAAACCTCC 19

IGTCTATTTTGTAAACCTCC 19

IGTCTATTTGTAAACCTCC 19

IGTCTATTTTGTAAACCTCC 19

IGTCTATTTTGTAAACCTCC 19

IGTCTATTTGTAAACCTCC 19

IGTCTATTTTGTAAACCTCC 19

IGTCTATTTGTAAACCTCC 19

IGTCTATTTTGTAAACCTCC 19

IGTCTATTTTGTAAACCTCC 19

IGTCTATTTTGTAAACCTCC 19

IGTCTATTTTGTAAACCTCC 19

IGTCTATTTGTAAACCTCC 19

IGTCTATTTGTAAACCTCC 19

IGTCTATTTTGTAAACCTCC 19

IGTCTATTTGTAAACCTCC 19

IGTCTATTTGTAAACCTCC 19

IGTCTATTTGTAAACCTCC 19

IGTCTATTTGTAAACCTCC 19

IGTCTATTTTGTAAACCTCC 19

IGTCTATTTTGTAAACCTCC 19

IGTCTATTTTGTAAACCTCC 19

IGTCTATTTTGTAAACCTCC 19

IGTCTATTTTGTAAACCTCC 19

IGTCTATTTTGTAAACCTCC 19

IGTCTATTTGTAAACCTCC 19

IGTCTATTTTGTAAACCTCC 19

IGTCTATTTTGTAAACCTCTTGTAAACCTCC 19

IGTCTATTTTTTTTTTTTTAAACCTCC 19

IGTCTATTAAACCTCTAAACCTCTTTTTTTAAACCTTTTTTAAACCTTTTTAAACCTTTTTAAACCTTTTTAAAC
```

Query Match
Query Match
Best Local Similarity 100.0%; Pred. No. 69;
Matches 19; Conservative 0; Mismatches 0; Indels 0; Gaps

ઠે

~

ö

```
Result
No.
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      Database
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           Post-processing: Minimum Match 0%
Maximum Match 100%
Listing first 45 summaries
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            Minimum DB seq length: 0 Maximum DB seq length: 60
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        Sequence:
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 Title:
Perfect score:
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      Total number of hits satisfying chosen parameters:
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     Searched:
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       Scoring table:
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   Run on:
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             OM nucleic - nucleic search, using sw model
                                                                                                                           იი
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              Pred. No. is the number of results predicted by chance to have a score greater than or equal to the score of the result being printed, and is derived by analysis of the total score distribution.
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  Score
       Query
Match Length DB
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            IDENTITY_NUC
Gapop 10.0 , Gapext 1.0
         100.0
1100.0
1100.0
1100.0
1100.0
1100.0
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
184.2
1
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 US-09-701-583A-7
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  4708233 seqs, 24227607955 residues
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        1 gtctattttgtaaacctcc 19
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     March
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      GenEmbl: *
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       gb_pat:
gb_p1:
gb_p1:
gb_r:
gb_ro:
gb_sc:
gb_sc:
gb_un:
gb_un:
gb_vi:
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  GenCore version 5.1.6
Copyright (c) 1993 - 2005 Compugen Ltd.
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   gb_btg:*
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         gb_om:*
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               8, 2005, 10:14:31 ; Search time 1443 Seconds (without alignments) 638.010 Million cell updates/sec
         A88380
A90347
                             AB8381
AD234904
AX008975
BD0656894
CQ665894
CQ6648820
CQ548820
CQ5488217
AX704643
AR355892
                                                                                                                                                                                                                                                                                                               BD234903
AX008974
BD065893
AX113805
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  Ħ
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         SUMMARIES
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      1981570
A88380 Sequence 52
A90347 Sequence 52
BD234903 A method
AX008974 Sequence
BD065893 An antise
AX113805 Sequence 52
A90348 Sequence 52
A90348 Sequence 52
BD234904 A method
AX008975 Sequence
BD065894 An antise
CQ054933 Sequence
CQ054933 Sequence
CQ0548820 Sequence
AX043439 Sequence
AX043439 Sequence
AX704643 Sequence
AX355892 Sequence
AX55892 Sequence
AX537448 Sequence
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  Description
```

ALIGNMENTS

RESULT 2 A90347 LOCUS DEFINITION ACCESSION VERSION VERSION KEYPORDS SOURCE SOURCE ORGANISM REFERENCE	Query Match Best Local; Matches 1: Qy 1 Db 1	SOURCE ORGANISM REFERENCE AUTHORS TITLS TITLS JOURNAL FEATURES SOURCE ORIGIN	RESULT 1 A88380 LOCUS DEFINITION ACCESSION VERSION VERSION KEYWORDS
A90347 A90347 A90347 A90347 A90347 A90347.1 GI:6738861 unidentified unidentified unclassified. 1 (bases 1 to 19)	h 100.0%; Score 19; DB 6; Similarity 100.0%; Pred. No. 1.3e+03; 19; Conservative 0; Mismatches 0; GTCTATTTGTAAACCTCC 19	unidentified unidentified unidentified. 1 (bases 1 to 19) 1 (bases 1 to 19) 1 (bases 1 to 19) ANTISENSE OLIGONUCLEOTIDE PREPARATION METHOD PATENT: WO 9833904-A 528 06-AUG-1998; BIOGNOSTIK GES (DE); BRYSCH WOLFGANG (DE) Location/Qualifiers 1. 19 /organism="unidentified" /mol type="unassigned DNA" /db_xref="taxon:32644"	A88380 19 bp DNA Sequence 528 from Patent WO9833904. A88380 A88380.1 GI:6736950
linear	Length 19; Indels	ВТНОД	linear
PAT	0;		A PAT
PAT 22-JAN-2000	Gaps		PAT 22-JAN-2000
000	0;		000